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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,433	10/01/2003	Arpi Matossian-Rogers	2003_1279	5502

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EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/674,433	MATOSSIAN-ROGERS, ARPI	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,14,15 and 17-30* is/are pending in the application.

4a) Of the above claim(s) *1-10,12,14,15 and 17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 2/20/08 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/20/07 has been entered.

Claims 29 and 30 have been amended.
Claims 1-10, 12, 14-15, and 17-30 are pending.

Claims 1-10, 12, 14-15, and 17-28 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 29-30 are being acted upon.

2. The rejection of the claims under 35 U.S.C. 112 second paragraph, and under 112 first paragraph for new matter are withdrawn in view of Applicant’s amendment to the claims.

3. In view of Applicant’s amendment, the rejection of the claims under 35 U.S.C. 112 first paragraph for lack of enablement is withdrawn. However, Applicant’s arguments relevant to the new grounds of rejection will be addressed below.

4. The following are new grounds of rejection.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 29-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could function to treat conditions where hyperinsulinaemia and insulin resistance are present by administering an antibody capable of binding an anti-T cell receptor antibody and a GPI linkage epitope.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

The instant method involves treating conditions wherein hyperinsulinaemia and insulin resistance are present by administering an antibody that binds to an anti-TCR antibody and a GPI linkage epitope. The instant specification demonstrates that said antibodies bind to alpha cells and modulate insulin secretion. The specification further demonstrates that said antibodies are present in patients with IDDM. The instant

specification states on pg. 36 that the injection of the antibody will be designed to prevent the development of autoantibodies of the same specificity by a feedback mechanism suppressing existing B cells, or by an idiotypic network of antibody development giving rise to protective mechanisms. Thus, the claimed invention involves administration of a supposedly pathogenic autoantibody, in order to invoke a suppressive anti-idiotypic response that suppresses the generation of said pathogenic autoantibodies. WO 2007/01786 (of record) demonstrates that administration of peptide fragments consisting of the CDR regions of autoantibodies that binds to an anti-TCR antibody and a GPI linkage epitope improve glycemic control in subjects with type II diabetes. WO 2007/01786 teaches that the peptides function to induce antibodies that specifically bind to the pathogenic autoantibodies aiding in their removal.

However, the instant claims are drawn to a method of treatment comprising administering an intact antibody, or an antigen binding fragment thereof such as a Fab fragment. This is different than administering a non-antigen binding CDR peptide, as is shown to be effective in WO 2007/01786. The CDR region of an intact antibody is a very small part of the overall structure of an antibody. For example, administration of an intact antibody, particularly across species, results in a complicated range of anti-isotype and anti-allotype specificities, in addition to anti-idiotypic specificities (see Skaletsky, page 4). Thus, the intact antibody might not function to generate a sufficient idiotypic response which is essential for removal of the pathogenic autoantibodies.

Furthermore, given the fact that the claimed treatment involves administering the supposed pathogenic antibody, it seems extremely unpredictable as to whether the antibody would be able to function in a suppressive feedback mechanism, as asserted by Applicant, without itself also inhibiting insulin production and exacerbating diabetes. For example, in SLE it is known that CDR peptides derived from anti-DNA autoantibodies suppress generation of said autoantibodies and inhibit disease (see Luger et al.). In contrast, Luger et al. teach that administration of the intact pathogenic autoantibody itself results in disease exacerbation. Thus, based on the state of art, it is apparent that it is extremely unpredictable as to whether an intact pathogenic autoantibody can function to suppress autoimmune disease in the same manner as a CDR peptide

derived therefrom. Thus, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claims. However, the instant specification does not provide any working examples demonstrating the effectiveness of administering the antibodies in generating suppressive feedback mechanisms or treatment of disease. Accordingly, the method as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

Applicant's arguments, and the declaration of Inventor Matossian-Rogers, filed 12/20/07, have been fully considered, but they are not persuasive.

Applicant argues, and the declaration of Matossian-Rogers states that those working in the field would expect that an entire antibody molecule would be at least as good as a short CDR peptide at generating neutralizing antibodies.

However, as noted above, immunization with an intact antibody results in a complicated range of anti-isotypic and anti-allotypic specificities, in addition to antibodies specific to the idiotypic or CDR regions. Thus, it is not clear that administration of an intact antibody would be as efficient in generated antibodies specific to the CDR regions, which is essential for neutralization of the pathogenic antibody.

Applicant further argues, and the declaration of Matossian-Rogers states that the administration of the pathogenic antibody would not be expected to worsen the patients condition, since the dose would be small. Additionally, Applicant asserts that the use of claimed antibodies is analogous to the treatment of rheumatoid arthritis with anti-CD52 antibodies and to administration of pathogenic anti-D antibody to Rh negative mothers.

As an initial matter, it is noted that the instant claims are not limited to administering a small dose of said pathogenic antibody. Furthermore, it is the Examiner's position that the administration of the pathogenic anti-TCR antibody is not analogous to the administration of anti-CD52 antibodies or anti-D antibodies, as asserted by Applicant. Anti-CD52 antibodies are administered to deplete T and B cells in patients with rheumatoid arthritis. Said anti-CD52 antibodies are not pathogenic autoantibodies themselves, as in the case of the

present invention. Furthermore, regarding anti-D antibody administration to Rh negative mothers, said antibodies are therapeutically administered at a dose calculated so as to bind to and deplete Rh+ cells that are found in the mothers circulation, leaving very little antibody that could potentially cross the placenta and act in a pathogenic manner in the fetus. In contrast, the instant invention involves administration of a pathogenic insulin modulating antibody in order to induce suppressive feedback mechanisms, and said antibody will directly be exposed to the endogenous autoantigen in the individual. This situation is most analogous to the experiments described above by Luger et all involving administration of intact pathogenic autoantibodies, or peptide CDR regions derived therefrom. Luger et al. demonstrate that CDR peptides derived from pathogenic autoantibodies suppress autoimmune disease, while in contrast, administration of the intact pathogenic autoantibodies themselves exacerbates disease. Thus, based on the state of art, it is apparent that it is extremely unpredictable as to whether an intact pathogenic autoantibody can function to suppress autoimmune disease in the same manner as a CDR peptide derived therefrom. Applicant has not provided any evidence that administration of an intact pathogenic autoantibody can function to induce suppressive feedback mechanisms and inhibit disease.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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